

## WHAT IS CLAIMED IS:

## 1. A composition comprising:

(a) a virus-like particle; and

(b) at least one immunostimulatory substance;

wherein said immunostimulatory substance is bound to said virus-like particle, and wherein said immunostimulatory substance is an unmethylated CpG-containing oligonucleotide, wherein the CpG motif of said unmethylated CpG-containing oligonucleotide is part of a palindromic sequence, and wherein said palindromic sequence is flanked at its 3'-terminus and at its 5'-terminus by less than 10 guanosine entities.

2. The composition of claim 1 further comprising at least one antigen, wherein said antigen is bound to said virus-like particle.

3. The composition of claim 2, wherein said at least one antigen or antigenic determinant is bound to said virus-like particle by at least one covalent bond, preferably wherein said covalent bond is a non-peptide bond.

4. The composition of claim 2, wherein said at least one antigen or antigenic determinant is fused to said virus-like particle.

5. The composition of any one of claims 2 to 4, wherein said virus-like particle comprises at least one first attachment site and wherein said antigen or antigenic determinant further comprises at least one second attachment site being selected from the group consisting of:

(a) an attachment site not naturally occurring with said antigen or antigenic determinant; and

(b) an attachment site naturally occurring with said antigen or antigenic determinant;

and wherein said binding of said antigen or antigenic determinant to said virus-like particle is effected through association between said first attachment

site and said second attachment site, wherein preferably said association is through at least one non-peptide bond.

- 5           6. The composition of claim 5, wherein said antigen or antigenic determinant and said virus-like particle interact through said association to form an ordered and repetitive antigen array.
- 10           7. The composition of claim 5 or 6, wherein said first attachment site comprises, or preferably consists of, an amino group or a lysine residue.
8. The composition of any of the claims 5 to 7, wherein said second attachment site comprises, or preferably consists of, a sulfhydryl group or a cysteine residue.
- 15           9. The composition of any of the claims 5 to 8, wherein said first attachment site is a lysine residue and said second attachment site is a cysteine residue.
10. The composition of any of the claims 5 to 9, wherein said first attachment site is an amino group and said second attachment site is a sulfhydryl group.
- 20           11. The composition of any one of claims 2 to 10, wherein said antigen is selected from the group consisting of:
- (a)     polypeptides;
- (b)     carbohydrates;
- (c)     steroid hormones; and
- 25           (d)     organic molecules.
12. The composition of any one of claims 2 to 11, wherein said antigen is an organic molecule, and wherein preferably said organic molecule is selected from the group consisting of:
- 30           (a)     codeine;
- (b)     fentanyl;
- (c)     heroin;
- (d)     morphium;

- 5 (e) amphetamine;  
(f) cocaine;  
(g) methylenedioxymethamphetamine;  
(h) methamphetamine;  
(i) methylphenidate;  
(j) nicotine;  
(k) LSD;  
(l) mescaline;  
(m) psilocybin; and  
10 (n) tetrahydrocannabinol.

13. The composition of any one of claims 2 to 1, wherein said antigen is derived from the group consisting of:

- 15 (a) viruses;  
(b) bacteria;  
(c) parasites;  
(d) prions;  
(e) tumors;  
(f) self-molecules;  
20 (g) non-peptidic hapten molecules  
(h) allergens; and  
(i) hormones.

25 14. The composition of claim 13, wherein said antigen is a tumor antigen, and wherein preferably said tumor antigen is selected from the group consisting of:

- 30 (a) Her2;  
(b) GD2;  
(c) EGF-R;  
(d) CEA;  
(e) CD52;  
(f) CD21;  
(g) human melanoma protein gp100;  
(h) human melanoma protein melan-A/MART-1;

- (i) tyrosinase;
- (j) NA17-A nt protein;
- (k) MAGE-3 protein;
- (l) p53 protein;
- 5 (m) HPV16 E7 protein;
- (n) human melanoma MelanA peptide;
- (o) human melanoma MelanA peptide analogue;
- (p) HIV polypeptide; and
- (q) antigenic fragments of any of the tumor antigens from (a) to (p).

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15. The composition of any one of claims 2 to 14, wherein said antigen is bound to said virus-like particle by way of a linking sequence.

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16. The composition of any one of claims 2 to 15, wherein said antigen comprises a cytotoxic T cell epitope, a Th cell epitope or a combination of at least two of said epitopes, wherein said at least two epitopes are bound directly or by way of a linking sequence, and wherein preferably said cytotoxic T cell epitope is a viral or a tumor cytotoxic T cell epitope.

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17. The composition of any one of the preceding claims, wherein said unmethylated CpG-containing oligonucleotide comprises 10 to 30 nucleotides.

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18. The composition of any one of the preceding claims, wherein said palindromic sequence is GACGATCGTC (SEQ ID NO: 1).

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19. The composition of any one of the preceding claims, wherein said palindromic sequence is flanked at its 5'-terminus by at least 3 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

20. The composition of 18, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGACGATCGTCGGGGGG ((SEQ ID NO: 2);

- (b) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);
- (c) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (d) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (e) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 6);
- 5 (f) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7);
- (g) GGGGGGGGGGACGATCGTCGGGGGGGGG ((SEQ ID NO: 8);
- and
- (h) GGGGGGCGACGACGATCGTCGTCGGGGGGG ((SEQ ID NO: 9).

10 21. The composition of claim any one of claims 1 to 18, wherein said palindromic sequence is flanked at its 5'-terminus by at least 4 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

15 22. The composition of claim 18, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);
- (b) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (c) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- 20 (d) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 6);
- (e) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7); and
- (f) GGGGGGGGGGACGATCGTCGGGGGGGGG ((SEQ ID NO: 8).

25 23. The composition of any one of claims 1 to 18, wherein said palindromic sequence is flanked at its 5'-terminus by at least 5 and at most 8 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 8 guanosine entities.

30 24. The composition of claim 18, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (b) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (c) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 6); and

(d) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7).

25. The composition of claim 18, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence of SEQ ID NO: 7.

26. The composition of any one of the preceding claims, wherein said unmethylated CpG-containing oligonucleotide contains one or more phosphorothioate modifications of the phosphate backbone or wherein each phosphate moiety of said phosphate backbone of said oligonucleotide is a phosphorothioate modification.

27. The composition of any one of the preceding claims, wherein said unmethylated CpG-containing oligonucleotide is non-covalently bound to said virus-like particle.

28. The composition of any one of claims 1 to 26, wherein said unmethylated CpG-containing oligonucleotide is bound to a virus-like particle site selected from the group consisting of an oligonucleotide binding site, a DNA binding site and a RNA binding site.

29. The composition of claim 28, wherein said oligonucleotide binding site is a non-naturally occurring oligonucleotide binding site.

30. The composition of any one of the preceding claims, wherein said unmethylated CpG-containing oligonucleotide, is selected from

- (a) a recombinant oligonucleotide;
- (b) a genomic oligonucleotide;
- (c) a synthetic oligonucleotide;
- (d) a plasmid-derived oligonucleotide;
- (e) a single-stranded oligonucleotide; and
- (f) a double-stranded oligonucleotide.

31. The composition of any one of the preceding claims, wherein said virus-like particle lacks a lipoprotein-containing envelope.

32. The composition of any one of the preceding claims, wherein said virus-like particle is selected from the group consisting of:

- (a) recombinant proteins of Hepatitis B virus;
- (b) recombinant proteins of measles virus;
- (c) recombinant proteins of Sinbis virus;
- (d) recombinant proteins of Rotavirus;
- (e) recombinant proteins of Foot-and-Mouth-Disease virus;
- (f) recombinant proteins of Retrovirus;
- (g) recombinant proteins of Norwalk virus;
- (h) recombinant proteins of human Papilloma virus;
- (i) recombinant proteins of BK virus;
- (j) recombinant proteins of bacteriophages;
- (k) recombinant proteins of RNA-phages;
- (l) recombinant proteins of Q $\beta$ -phage;
- (m) recombinant proteins of GA-phage;
- (n) recombinant proteins of fr-phage;
- (o) recombinant proteins of AP 205-phage;
- (p) recombinant proteins of Ty; and
- (q) fragments of any of the recombinant proteins from (a) to (p).

33. The composition of any of the preceding claims, wherein said virus-like particle is the Hepatitis B virus core protein or the BK virus VP1 protein.

34. The composition of any one of claims 1 to 32, wherein said virus-like particle comprises, or alternatively consists essentially of, or alternatively consists of recombinant proteins, or fragments thereof, of a RNA-phage, wherein preferably said RNA-phage is selected from the group consisting of:

- (a) bacteriophage Q $\beta$ ;
- (b) bacteriophage R17;
- (c) bacteriophage fr;

- (d) bacteriophage GA;
- (e) bacteriophage SP;
- (f) bacteriophage MS2;
- (g) bacteriophage M11;
- 5 (h) bacteriophage MX1;
- (i) bacteriophage NL95;
- (j) bacteriophage f2;
- (k) bacteriophage PP7; and
- 10 (l) bacteriophage AP205.

35. The composition of any one of the preceding claims, wherein said virus-like particle comprises, or alternatively consists essentially of, or alternatively consists of recombinant proteins, or fragments thereof, of bacteriophage Q $\beta$  or bacteriophage AP205.

36. A method for enhancing an immune response in an animal comprising introducing into said animal a composition of any one of the preceding claims.

37. A method of producing a composition for enhancing an immune response in an animal comprising a virus-like particle and an immunostimulatory substance bound to said virus-like particle which comprises:

- (a) incubating said virus-like particle with said immunostimulatory substance;
- (b) adding RNase; and
- 25 (c) purifying said composition;

wherein said immunostimulatory substance is an unmethylated CpG-containing oligonucleotide, wherein the CpG motif of said unmethylated CpG-containing oligonucleotide is part of a palindromic sequence, and wherein said palindromic sequence is flanked at its 3'-terminus and at its 5'-terminus by less than 10 guanosine entities.

38. The method of claim 37, wherein said unmethylated CpG-containing oligonucleotide comprises 10 to 30 nucleotides.



39. The method of claim 37, wherein said palindromic sequence is GACGATCGTC (SEQ ID NO: 1).

40. The method of any one of claim 37 to 39, wherein said palindromic sequence is flanked at its 5'-terminus by at least 3 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

41. The method of claim 39, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGACGATCGTCGGGGGG ((SEQ ID NO: 2);
- (b) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);
- (c) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (d) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (e) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 6);
- (f) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7);
- (g) GGGGGGGGGGACGATCGTCGGGGGGGGG ((SEQ ID NO: 8);
- and
- (h) GGGGGGCGACGACGATCGTCGTCGGGGGGGG ((SEQ ID NO: 9).

42. The method of any one of claim 37 to 39, wherein said palindromic sequence is flanked at its 5'-terminus by at least 4 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

43. The method of claim 37, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);
- (b) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (c) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (d) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 6);
- (e) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7); and

(f) GGGGGGGGGGACGATCGTCGGGGGGGGG ((SEQ ID NO: 8).

44. The method of any one of claim 37 to 39, wherein said palindromic sequence is flanked at its 5'-terminus by at least 5 and at most 8 guanosine entities and  
5 wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 8 guanosine entities.

45. The method of claim 39, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- 10 (a) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);  
(b) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);  
(c) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO:6); and  
(d) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7).

15 46. The method of claim 39, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence of SEQ ID NO: 7.

47. The method of any one of claims 37 to 46, wherein said unmethylated CpG-containing oligonucleotide contains one or more phosphorothioate modifications  
20 of the phosphate backbone or wherein each phosphate moiety of said phosphate backbone of said oligonucleotide is a phosphorothioate modification.

48. The method of claim 37, wherein said virus-like particle is produced in a bacterial expression system.

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49. The method of claim 37, wherein said RNase is RNase A.

50. The method of any of claims 37 to 49, further comprising the step of binding an antigen or antigenic determinant to said virus-like particle.

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51. The method of claim 50, wherein said antigen or antigenic determinant is bound to said virus-like particle before incubating said virus-like particle with said immunostimulatory substance.

52. The method of claim 50, wherein said antigen or antigenic determinant is bound to said virus like particle after purifying said composition.

5 53. A method of producing a composition for enhancing an immune response in an animal comprising a virus-like particle and an immunostimulatory substance bound to said virus-like particle which comprises:

- (a) incubating said virus-like particle with RNase;
- (b) adding said immunostimulatory substance; and
- 10 (c) purifying said composition

wherein said immunostimulatory substance is an unmethylated CpG-containing oligonucleotide, wherein the CpG motif of said unmethylated CpG-containing oligonucleotide is part of a palindromic sequence, and wherein said palindromic sequence is flanked at its 3'-terminus and at its 5'-terminus by less  
15 than 10 guanosine entities.

54. The method of claim 53, wherein said unmethylated CpG-containing oligonucleotide comprises 10 to 30 nucleotides.

20 55. The method of claim 53, wherein said palindromic sequence is GACGATCGTC (SEQ ID NO: 1).

56. The method of any one of claim 53 to 55, wherein said palindromic sequence is flanked at its 5'-terminus by at least 3 and at most 9 guanosine entities and  
25 wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

57. The method of claim 55, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- 30 (a) GGGGACGATCGTCGGGGGG ((SEQ ID NO: 2);
- (b) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);
- (c) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (d) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);

- (e) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO:6);
- (f) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 7);
- (g) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 8);
- and
- (h) GGGGGGCGACGACGATCGTCGTCGGGGGGG ((SEQ ID NO: 9).

58. The method of any one of claim 53 to 55, wherein said palindromic sequence is flanked at its 5'-terminus by at least 4 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

59. The method of claim 55, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);
- (b) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (c) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (d) GGGGGGGGACGATCGTCGGGGGG ((SEQ ID NO:6);
- (e) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7); and
- (f) GGGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 8).

60. The method of any one of claim 53 to 55, wherein said palindromic sequence is flanked at its 5'-terminus by at least 5 and at most 8 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 8 guanosine entities.

61. The method of claim 55, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (b) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (c) GGGGGGGGACGATCGTCGGGGGG ((SEQ ID NO:6); and
- (d) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7).

62. The method of claim 55, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence of SEQ ID NO: 7.

5 63. The method of any one of claim 53 to 62, wherein said unmethylated CpG-containing oligonucleotide contains one or more phosphorothioate modifications of the phosphate backbone or wherein each phosphate moiety of said phosphate backbone of said oligonucleotide is a phosphorothioate modification.

10 64. The method of claim 53, wherein said virus-like particle is produced in a bacterial expression system.

65. The method of claim 53, wherein said RNase is RNase A.

15 66. The method of any of claims 53 to 65, further comprising the step of binding an antigen or antigenic determinant to said virus-like particle.

67. The method of claim 66, wherein said antigen or antigenic determinant is bound to said virus-like particle before incubating said virus-like particle with said RNase.

20 68. The method of claim 66, wherein said antigen or antigenic determinant is bound to said virus like particle after purifying said composition.

25 69. A method of producing a composition for enhancing an immune response in an animal comprising a virus-like particle and an immunostimulatory substance bound to said virus-like particle which comprises:

- (a) disassembling said virus-like particle;
- (b) adding said immunostimulatory substance; and
- (c) reassembling said virus-like particle

30 wherein said immunostimulatory substance is an unmethylated CpG-containing oligonucleotide, wherein the CpG motif of said unmethylated CpG-containing oligonucleotide is part of a palindromic sequence, and wherein said palindromic sequence is flanked at its 3'-terminus and at its 5'-terminus by less than 10 guanosine entities.

70. The method of claim 69, wherein said unmethylated CpG-containing oligonucleotide comprises 10 to 30 nucleotides.

5 71. The method of claim 69, wherein said palindromic sequence is GACGATCGTC (SEQ ID NO: 1).

72. The method of any one of claim 69 to 71, wherein said palindromic sequence is flanked at its 5'-terminus by at least 3 and at most 9 guanosine entities and  
10 wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

73. The method of claim 71, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- 15 (a) GGGGACGATCGTCGGGGGG ((SEQ ID NO: 2);  
(b) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);  
(c) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);  
(d) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);  
(e) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 6);  
20 (f) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7);  
(g) GGGGGGGGGGACGATCGTCGGGGGGGGG ((SEQ ID NO: 8);  
and  
(h) GGGGGGCGACGACGATCGTCGTCGGGGGGG ((SEQ ID NO: 9).

25 74. The method of any one of claim 69 to 71, wherein said palindromic sequence is flanked at its 5'-terminus by at least 4 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

30 75. The method of claim 71, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);  
(b) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);

- (c) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (d) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO:6);
- (e) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7); and
- (f) GGGGGGGGGGACGATCGTCGGGGGGGGG ((SEQ ID NO: 8).

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76. The method of any one of claim 69 to 71, wherein said palindromic sequence is flanked at its 5'-terminus by at least 5 and at most 8 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 8 guanosine entities.

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77. The method of claim 71, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);
- (b) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);
- (c) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO:6); and
- (d) GGGGGGGGGACGATCGTCGGGGGGGG ((SEQ ID NO: 7).

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78. The method of claim 71, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence of SEQ ID NO: 7.

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79. The method of any one of claim 69 to 78, wherein said unmethylated CpG-containing oligonucleotide contains one or more phosphorothioate modifications of the phosphate backbone or wherein each phosphate moiety of said phosphate backbone of said oligonucleotide is a phosphorothioate modification.

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80. The method of any of claims 69 to 79 further comprising removing nucleic acids of said disassembled virus-like particle.

81. The method of any of claims 69 to 79 further comprising purifying said composition after reassembly.

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82. The method of any of claims 69 to 81, further comprising the step of binding an antigen or antigenic determinant to said virus-like particle.

83. The method of claim 82, wherein said antigen or antigenic determinant is bound to said virus-like particle before disassembling said virus-like particle.

5 84. The method of claim 50, wherein said antigen or antigenic determinant is bound to said virus like particle after reassembling said virus-like particle.

85. A method of producing a composition for enhancing an immune response in an animal comprising a virus-like particle and an immunostimulatory substance  
10 bound to said virus-like particle which comprises:

- (a) incubating said virus-like particle with solutions comprising metal ions capable of hydrolizing the nucleic acids of said virus-like particle;
- (b) adding said immunostimulatory substance; and
- (c) purifying said composition

15 wherein said immunostimulatory substance is an unmethylated CpG-containing oligonucleotide, wherein the CpG motif of said unmethylated CpG-containing oligonucleotide is part of a palindromic sequence, and wherein said palindromic sequence is flanked at its 3'-terminus and at its 5'-terminus by less than 10 guanosine entities.

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86. The method of claim 85, wherein said unmethylated CpG-containing oligonucleotide comprises 10 to 30 nucleotides.

25 87. The method of claim 85, wherein said palindromic sequence is GACGATCGTC (SEQ ID NO: 1).

88. The method of any one of claim 85 to 87, wherein said palindromic sequence is flanked at its 5'-terminus by at least 3 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at  
30 most 9 guanosine entities.

89. The method of claim 87, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from



- (a) GGGGACGATCGTCGGGGGG ((SEQ ID NO: 2);  
(b) GGGGGACGATCGTCGGGGGG ((SEQ ID NO: 3);  
(c) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);  
(d) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);  
5 (e) GGGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 6);  
(f) GGGGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 7);  
(g) GGGGGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 8);  
and  
(h) GGGGGGCGACGACGATCGTCGTCGGGGGG ((SEQ ID NO: 9).

10 90. The method of any one of claim 85 to 87, wherein said palindromic sequence is flanked at its 5'-terminus by at least 4 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus by at least 6 and at most 9 guanosine entities.

15 91. The method of claim 87, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGACGATCGTCGGGGGG (SEQ ID NO: 3);  
(b) GGGGGGACGATCGTCGGGGGG (SEQ ID NO: 4);  
20 (c) GGGGGGGACGATCGTCGGGGGG (SEQ ID NO: 5);  
(d) GGGGGGGGACGATCGTCGGGGGG (SEQ ID NO: 6);  
(e) GGGGGGGGGACGATCGTCGGGGGG (SEQ ID NO: 7); and  
(f) GGGGGGGGGGACGATCGTCGGGGGG (SEQ ID NO: 8).

25 92. The method of any one of claim 85 to 87, wherein said palindromic sequence is flanked at its 5'-terminus of at least 5 and at most 8 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus of at least 6 and at most 8 guanosine entities.

30 93. The method of claim 87, wherein said unmethylated CpG-containing oligonucleotide has a nucleic acid sequence selected from

- (a) GGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 4);  
(b) GGGGGGGACGATCGTCGGGGGG ((SEQ ID NO: 5);

- (c) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO:6); and
- (d) GGGGGGGGACGATCGTCGGGGGGG ((SEQ ID NO: 7).

94. The method of claim 87, wherein said unmethylated CpG-containing  
5 oligonucleotide has a nucleic acid sequence of SEQ ID NO: 7.

95. The method of any one of claim 85 to 94, wherein said unmethylated CpG-  
containing oligonucleotide contains one or more phosphorothioate modifications  
of the phosphate backbone or wherein each phosphate moiety of said phosphate  
10 backbone of said oligonucleotide is a phosphorothioate modification.

96. The method of claim 85, wherein said metal ions are selected from the group  
consisting of:

- (a) zinc (Zn) ions;
- (b) copper (Cu) ions;
- (c) iron (Fe) ions; and
- (d) any mixtures of at least one ion of (a), (b) and/or (c).

97. The method of any of claims 85 to 96, further comprising the step of binding an  
20 antigen or antigenic determinant to said virus-like particle.

98. The method of claim 97, wherein said antigen or antigenic determinant is bound to  
said virus-like particle before incubating said virus-like particle with solutions  
comprising metal ions.

99. The method of claim 50, wherein said antigen or antigenic determinant is bound to  
said virus like particle after adding said immunostimulatory substance and after  
purifying said composition.

100. A vaccine comprising an immunologically effective amount of the  
composition of any one of claim 1 to 31 together with a pharmaceutically  
acceptable diluent, carrier or excipient.

101. The vaccine of claim 100 further comprising an adjuvant.

102. A method of immunizing or treating an animal comprising administering to said animal an immunologically effective amount of the vaccine of any one of claim 100 or 101.

103. The method of claim 102, wherein said animal is a mammal.

104. The method of claim 102, wherein said mammal is a human.

105. A method of immunizing or treating an animal comprising priming a T cell response in said animal by administering an immunologically effective amount of the vaccine of claim 100.

106. The method of claim 105, further comprising the step of boosting the immune response in said animal, wherein preferably said boosting is effected by administering an immunologically effective amount of a vaccine of claim 100 or an immunologically effective amount of a heterologous vaccine, wherein even more preferably said heterologous vaccine is a DNA vaccine.

107. A method of immunizing or treating an animal comprising the steps of priming a T cell response in said animal, and boosting a T cell response in said animal, wherein said boosting is effected by administering an immunologically effective amount of the vaccine of claim 100.

108. The method of claim 107, wherein said priming is effected by administering an immunologically effective amount of a vaccine of claim 100 or an immunologically effective amount of a heterologous vaccine, and wherein even more preferably said heterologous vaccine is a DNA vaccine.

109. An isolated nucleic acid molecule comprising, or alternatively consisting essentially of, or alternatively consisting of an unmethylated CpG-containing oligonucleotide, wherein the CpG motif of said unmethylated CpG-containing

oligonucleotide is part of a palindromic sequence, wherein said palindromic sequence is GACGATCGTC (SEQ ID NO: 1), and said palindromic sequence is flanked at its 5'-terminus of at least 4 and at most 9 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus of at least 6 and at most 9 guanosine entities

110. The isolated nucleic acid molecule of claim 109, wherein said palindromic sequence is flanked at its 5'-terminus of at least 5 and at most 8 guanosine entities and wherein said palindromic sequence is flanked at its 3'-terminus of at least 6 and at most 8 guanosine entities.

111. An isolated nucleic acid molecule comprising, or alternatively consisting essentially of, or alternatively consisting of a polynucleotide having a nucleotide sequence selected from

- (a) GGGGGACGATCGTCGGGGGG (SEQ ID NO: 3);
- (b) GGGGGGACGATCGTCGGGGGG (SEQ ID NO: 4);
- (c) GGGGGGGACGATCGTCGGGGGG (SEQ ID NO: 5);
- (d) GGGGGGGGACGATCGTCGGGGGGG (SEQ ID NO: 6);
- (e) GGGGGGGGGACGATCGTCGGGGGGGG (SEQ ID NO: 7);
- (f) GGGGGGGGGGACGATCGTCGGGGGGGGG (SEQ ID NO: 8); and
- (g) a nucleotide sequence of at least 80% sequence identity, preferably at least 90% sequence identity, more preferred at least 95% sequence identity, most preferred at least 99% sequence identity with any of the nucleotide sequences listed of (a) to (f).

112. An isolated nucleic acid molecule comprising, or alternatively consisting essentially of, or alternatively consisting of a polynucleotide having a nucleotide sequence selected from

- (a) GGGGGGACGATCGTCGGGGGG (SEQ ID NO: 4);
- (b) GGGGGGACGATCGTCGGGGGGG (SEQ ID NO: 5);
- (c) GGGGGGGGACGATCGTCGGGGGGG (SEQ ID NO: 6); and
- (d) GGGGGGGGGACGATCGTCGGGGGGGG (SEQ ID NO: 7).

- (e) a nucleotide sequence of at least 80% sequence identity, preferably at least 90% sequence identity, more preferred at least 95% sequence identity, most preferred at least 99% sequence identity with any of the nucleotide sequences listed of (a) to (d).

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113. An isolated nucleic acid molecule comprising, or alternatively consisting essentially of, or alternatively consisting of a polynucleotide having a nucleotide sequence of SEQ ID NO: 7 or a nucleotide sequence of at least 80% sequence identity, preferably at least 90% sequence identity, more preferred at least 95% sequence identity, most preferred at least 99% sequence identity with SEQ ID NO: 7.

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